The Heart Attack & Stroke Prevention Center
Breaking ground with the Bale/Doneen Method

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Periodontal Disease and CHD – A Red Flag or Target of Therapy?

Atherosclerotic plaque rupture and subsequent thrombus formation is the perfect set up for a heart attack or ischemic stroke. It is clinically necessary to evaluate all opportunities that could lead to arterial wall inflammation which inevitably could lead to the atherosclerotic plaque lesion rupturing through the endothelial surface of the artery, allowing for a thrombus to form which can block the flow of blood, causing a clinical event. Inflammation is the cornerstone of atherothrombotic formation. Additionally, heart attacks and ischemic strokes are opportunistic problems- they occur in the presence of an inflammatory event. Periodontal disease is a bacterial infection of the periodontia that can quickly propel into the systemic vasculature system, creating an opportunity for endothelial and intima inflammation, subsequent plaque rupture and thrombus formation.

In 2005, Dr. Aramesh Saremi et al, published a prospective longitudinal study of 628 subjects to examine the effect of periodontal disease on overall and cardiovascular disease mortality in type 2 diabetics. ***(Saremi, Aramesh, MD. Periodontal Disease and Mortality in Type 2 Diabetes; Diabetes Care 28;27-32, 2005)***. Saremi et al evaluated 628 type 2 diabetic Pima Indians aged $\geq$ 35. Based on clinical exams and panoramic x-ray studies, the subjects were classified as having mild, moderate, and severe periodontal disease. Severe periodontal disease was defined as less than 15 teeth or a median bone loss score of <75% or a median attachment loss of $\geq$ 6 mm. During the median follow-up of 11 years, 204 subjects died. There was a linear, progressive association between severity of periodontal disease and death from ischemic heart disease and diabetic nephropathy.

After adjustments for age, sex, duration of diabetes, HgA1C, MACR, BMI, serum cholesterol HTN, electrocardiographic abnormalities and smoking, subjects with severe periodontal disease had 3.2 times higher risk (95% CI 1.1-9.3) of cardiac and renal mortality compared with the reference group (mild periodontal disease and moderate periodontal disease combined). The authors concluded that periodontal disease is a strong predictor of mortality from ischemic heart disease and diabetic nephropathy in Pima Indians with type 2 diabetes. This study demonstrates the value of assessing periodontal health in all type 2 diabetic subjects. Bale and Doneen also recognize that type 2 diabetes is a coronary risk equivalent. Therefore, anyone with type 2 diabetes or vascular disease is at increased risk for CV mortality in the presence of severe periodontal disease.

In 2007, treatment of periodontal disease and the effect of endothelial function was established by Tonetti, M, et al. The work of Tonetti and his team received recognition in the New England Journal of Medicine. ***(Tonetti, M, et al. Treatment of Periodontitis and Endothelial Function. N Engl J Med 2007;356;911-20).*** This piece of research assists to elucidate the fact that inflammation is vital in the pathogenesis of atherosclerosis and it is

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vitally important to identify the source of any low grade chronic systemic infection. Tonetti and his team set out to prove a cause and effect relationship between the treatment of periodontal disease and improved endothelial function. They randomly assigned 120 patients with severe periodontitis to either a community-based periodontal care clinic (n=59) or an intensive periodontal treatment center (n=61). Endothelial function using flow-mediated dilation and inflammatory biomarkers, coagulation markers and endothelial activation were evaluated before treatment and at periodic increments thereafter (1,7,30,60, and 180 days after treatment). Biomarkers included, but not limited to, PAI-1, hsCRP, Neutrophils, Von Willebrand factor, and IL6. The results were interesting in that, in the short term, systemic inflammation and endothelial dysfunction occurred as intensive periodontal treatment occurred. Six months after intensive therapy of periodontal disease, endothelial function was statistically improved. No cardiovascular events occurred in this study period. The significance of this trial for the Bale/Doneen method is that the act of treating periodontal disease can lend to short term exacerbation of systemic inflammation and the long term benefits of periodontal treatment yield endothelial stability. It is important to assess and treat all patients for cardiovascular risk prior to entering a periodontal treatment program. It is also important to appreciate the long term benefit of periodontal care on CV stability.

In 2008, the American Journal of Cardiology published a manuscript highlighting the relationship of periodontal disease, cardiovascular disease and systemic inflammation. The manuscript highlights the value of oral health screening in the context of cardiovascular risk assessment – thus calling for the recognition of self-reported oral health status as a risk factor for CBD. The authors recognize the NHLBI Family Intervention Trial for Heart Health (F.I.T. Heart) (n=421; mean age 48± 13.5yr without known cardiovascular disease or diabetes who underwent standardized assessment of oral health, lifestyle, CVD risk factors and inflammatory markers, including hs-CRP and Lp-PLA2. Periodontal disease was independently associated with being in the top Lp-PLA2 quartile versus the lower three (OR=1.9;95%CI=1.1-3.2) after adjustment for lifestyle and risk factors. The authors concluded that self-reported periodontal disease is independently associated with inflammation and common in persons who lack traditional CVD risk-factors. ***(Am J Cardiol. 2008 December 1; 102(11); 1509-1513).***

The oral health data was collected using the following standardized questions: 1. “Have you ever been informed that you have periodontal (gum) disease?”, 2. “Have you ever received treatment for periodontal disease?”, 3. “Do you have removable partial or complete dentures?”, and 4. “When was the last time you had your teeth cleaned?”. It is important to recognize that the observed associated between these self-reported histories of periodontal health and increased Lp-PLA2 levels remained statistically significant when controlling for age, sex, race, smoking, LDL Cholesterol and dietary saturated fat. The association between last dental cleaning >12 months and hsCRP level did not retain statistical merit after adjustment for age, sex, race, smoking, waist circumference and BMI. It was hypothesized that the lack of association between oral health and hsCRP after adjustment may be related to the fact that they controlled for MCI, smoking and

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other lifestyle factors. *The Bale/Doneen Method recognizes the fact that hsCRP is a marker of inflammation and not actually a player in the atherogenic disease process* ***(Circulation. 9/2/2008;118:1172-1182. Zacho J et al. N Engl J Med 10/30/2008; 359:1897-1908 Elliott, P., et. Al. JAMA, July 1,2009 – Vol. 302, No. 1:37-48).*** F.I.T. Heart adds value to the opportunity for the Bale/Doneen Method to add appropriate self reported oral health questions to their comprehensive history work sheet. This information is extremely valuable when assessing the individual needs and risks of the patient.

Carotid Intima Media thickness testing has been a "work horse" tool for all Bale/Doneen centers to identify atherosclerosis and monitor disease over time in the individual patient. Stefanie Piconi and team performed an analysis of the benefits of treating periodontal disease and associated benefits to endothelial dysfunction and reduction of carotid intima-media thickness. ***(Piconi, S., et al. Treatment of periodontal disease results in improvements in endothelial dysfunction and reduction of the carotid intima-media thickness. The FASEB Journal. Vol 23,fj.08-119578. April 2009).*** The premise of their research was to verify if the modification of periodontal treatment alone had the ability to impact inflammatory biomarkers, endothelial adhesion molecules, leukocyte activation markers and intima-media thickness.

The performed laboratory analysis and echo-Doppler carotid intima-media thickness testing on thirty-five otherwise healthy individuals who had mild to moderate pariodontopathy. Periodontal treatment resulted in a significant reduction of the total oral bacterial load and was associated with a significant resolve of inflammatory biomarkers and adhesion and activation proteins. Additionally, intima-media thickness was significantly diminished after treatment. (Protocols of cIMT were performed using the Mannheim IMT Consensus). A diminishing IMT was noted as early as 6 months after periodontal treatment and persisted throughout the study period (At the bifurcation: baseline=0.55$\pm$ 0.03 mm; 6 months =0.40$\pm$ 0.04mm; 12 months = 0.45$\pm$ 0.04mm; baseline vs 6 months, p=0.001, baseline vs 12 months; p=0.01). (1 cm from the bifurcation: baseline = 0.49$\pm$0.02mm; 6 months = 0.38$\pm$0.042mm; 12 months = 0.37$\pm$0.03mm; baseline vs 6 months: p=0.003; baseline vs 12 months: p<0.001). The authors make mention of the fatty streaks that are evident in early atherosclerotic development, containing macrophage-derived foam cells from circulating monocytes and CD4T cells. This monocyte/macrophage infiltration of the arterial wall is exacerbated by the infiltration of P. gingivalis which is a key player in severe periodontal disease states. Eradicating the bacterial infestation that occurs with periodontal disease has a positive effect on the arterial wall inflammation.

These data and others have resulted in the formalization of a consensus report by the American Journal of Cardiology and Journal of Periodontology which is aimed at providing health professionals, particularly cardiologists and periodontists, to understand and appreciate the link between atherosclerosis and periodontitis. ***(J Periodontal 2009; 80:1021-1032)***. This consensus document highlights the mechanisms behind the association between

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periodontitis and atherosclerotic cardiovascular disease – stating that: 1. Moderate to severe periodontitis increases the level of systemic inflammation and, 2. The bacteria present in

untreated periodontitis gum pockets create ulcerated epithelium both in the periodontal pockets and in intima atheromas. An indirect association establishes the belief that a pooling of risk factors lends to the severity of outcomes – ie: untreated periodontal disease in the presence of smoking, diabetes, obesity, hyper-lipidemia and hypertension equates to a synergistic state of inflammatory risk and CVD events. The Bale/Doneen Method is based on a disease treatment paradigm rather than a risk factor paradigm – lending to the effort to remove any risk (ie: periodontal disease) in individuals with atherosclerosis. Additionally, it is essential to screen patients for periodontal disease as part of a Bale/Doneen cardiovascular health assessment and history.

Most recently, a link was also established between metabolic syndrome, insulin resistance and periodontitis. Benguigui, C, et al, performed a cross-sectional stud with the goal of evaluating the clinical cluster of metabolic syndrome and clinical and biological abnormalities, including the subsequent exacerbation of metabolic syndrome and insulin resistance in the presence of periodontal disease and the impact on CHD. ***(J. Clin Periodontal 2010; 37:601-608).*** Benguigui et al evaluated 276 subjects, aged 35-74 years, and evaluated for metabolic syndrome criteria and HOMA index for insulin resistance. After adjustments were made, HOMA index remained directly associated with severe periodontitis (OR 53.97 CI: 1.22-12.9). They concluded that the relationship between metabolic abnormalities and periodontal disease was synergistic.

Lastly, we now have the opportunity to screen for periodontal bacterial growth via saliva prior to clinical symptomatology using the test developed by OralDNA Labs and Dr. Tom Nabors, D.D.S. Dr. Nabors' early work led to the development of OralDNA Labs in 2008 and subsequently maintains the position of Chief Dental Officer. His research is on-going based on biological markers that provide early identification of oral pathogens and genetic markers associated with periodontal disease. OralDNA Labs also offers the genetic detection of polymorphisms that occur in the IL-1 gene cluster. This SNP occurs in approximately 30% of the population. The importance here is that IL-1 positive subjects display an exaggerated response in the presence of specific disease associated bacteria thus displaying both increased local inflammation and systemic inflammatory markers. His work has enhanced the ability to clinically identify those at highest risk for this systemically inflammatory condition and his lab offers the unique opportunity for patients to be properly assessed for these pathogens and DNA risk. It is under the recommendation of the Bale/Doneen Method that all patients getting assessed for vascular wellness, receive the testing offered by OralDNA labs, under the medical direction of Dr. Tom Nabors.

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